

TUBERCULOSIS

Adverse events and treatment interruption in tuberculosis patients with and without HIV co-infection

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Thorax 2006;61:791-794. doi: 10.1136/thx.2006.058867

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Received 18 January 2006
Accepted 7 June 2006
Published Online First
14 July 2006

Background: Serious treatment associated adverse events are thought to occur more frequently in individuals with tuberculosis (TB) who are co-infected with HIV. A study was undertaken to assess the frequency of serious (grade III/IV) adverse events and interruption of anti-TB treatment in the era of effective antiretroviral therapy.

Methods: The incidence of serious adverse events was retrospectively compared in 312 individuals treated for TB, 156 of whom were co-infected with HIV.

Results: 111 HIV infected individuals (71%) received highly active antiretroviral therapy at the same time as anti-TB treatment. Serious adverse events were recorded in 40% HIV infected and 26% HIV uninfected individuals ($p=0.008$). Peripheral neuropathy and persistent vomiting were more common in co-infected patients ($p<0.001$; $p=0.006$), although all cause interruption of anti-TB treatment occurred with similar frequency in the two groups (13% in HIV infected patients and 15% in HIV uninfected patients; $p=0.74$). In 85% of HIV infected patients and 87% of HIV uninfected individuals this was due to hepatotoxicity, which typically presented within 2 months of starting treatment. The median delay in restarting treatment was 4 weeks, so most individuals required full TB re-treatment.

Conclusion: Despite a greater rate of serious (grade III/IV) adverse events among HIV infected individuals, discontinuation of anti-TB treatment occurred with a similar frequency in HIV infected and HIV uninfected individuals.

Although the response to anti-tuberculosis (TB) treatment among HIV co-infected patients is generally good, many require concurrent highly active antiretroviral therapy (HAART) to achieve a successful long term outcome.^{1,2} It has been reported that HIV/TB co-infected patients experience a higher rate of adverse drug reactions to treatment than those without HIV.³ Prior to the use of HAART, this may have reflected the additional toxicity of treatment for other opportunistic infections or that due to specific anti-TB agents such as thiacetazone.^{4,5} Few data exist in co-infected individuals since HAART has become widely available, although a very high rate of adverse drug reactions has been described.⁶ We hypothesised that, through careful selection of treatment regimens to minimise toxicity, the presence of HIV co-infection should have little impact on the frequency of serious (grade III/IV) adverse events, especially those causing treatment interruption, even if HAART was co-administered.

METHODS

Data were collected retrospectively at the North Middlesex, Royal Free, and University College London Hospitals, London. Consecutive unselected adult HIV infected individuals treated for TB between February 1997 and November 2003 were identified and compared with a control group of HIV uninfected individuals attending these treatment centres for TB treatment during the study period. Over this time the policy on testing for HIV infection of patients with TB changed from it being offered at physician discretion, based on an assessment of risk, to one of all patients being offered a test regardless of risk. To minimise possible selection bias we therefore included consecutive HIV uninfected individuals

from the end of the study period working backwards in time until the two groups were of an identical size.

Tuberculosis was diagnosed if a patient had (1) a positive culture for *Mycobacterium tuberculosis*; or (2) was culture negative but nucleic acid amplification assay positive (TB Strand Displacement Amplification assay, Becton-Dickinson, New Jersey, USA) with clinicoradiological features and response to treatment consistent with TB; or (3) had histological findings and response to treatment consistent with TB.

Retrospective case note review identified the occurrence of serious (grade III/IV) adverse drug reactions and episodes of treatment interruption. Treatment interruption was defined as any period in which anti-TB therapy was discontinued due to an adverse drug reaction. Hepatotoxicity was defined as liver transaminases (AST/ALT) rising to >5 times the upper limit of normal, or a rising bilirubin level.⁷ Liver function was routinely checked at baseline (along with assessment of hepatitis B and C status) and repeated at 2 weeks. In individuals with normal test results, further blood tests were performed only in the event of new symptoms. In patients with chronic liver disease, liver function was checked every second week for 2 months and those with abnormal liver function before treatment or at week 2 were re-checked every second week until they had normalised or were clearly stable. HIV infected individuals with TB generally had liver function tests monitored more frequently throughout their treatment course, although the frequency of this was at the discretion of

Abbreviations: HAART, highly active antiretroviral therapy; NRTI, nucleoside reverse transcriptase inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; TB, tuberculosis

the treating physician. Following discontinuation, treatment was recommenced according to national guidelines.⁷

Other adverse events were as documented by the treating clinician in the patient notes and graded by the investigators based on a standard classification system.⁸ The definitions of the most notable serious adverse events were: *hepatotoxicity* as described above; *peripheral neuropathy* as a marked decrease in sensation to the level of the knees or wrists; *arthralgia* as joint pain causing marked impairment of activities of daily living or mobility; *persistent vomiting* as vomiting of all food/fluids for 24 hours; and *rash* as vesiculation or moist desquamation or ulceration.

If anti-TB treatment had been discontinued, re-introduction was attempted sequentially in the order isoniazid, rifamycin, pyrazinamide, with the dose of each agent increased up to the therapeutic amount over 2 or 3 days with a period of 2 or 3 days of observation between restarting each agent.⁷ Data were recorded on a standard proforma and entered on a central database.

Prescription of HAART and anti-TB treatment was at the discretion of individual physicians using the treatment protocols then available. In all cases initial treatment of TB was rifamycin based and was adjusted according to availability of mycobacterial susceptibility testing. A typical regimen would start with a rifamycin plus isoniazid and pyrazinamide (ethambutol was routinely commenced at North Middlesex and Royal Free but not University College) for 2 months followed by a continuation phase of two drugs dependent on drug sensitivities. All patients receiving isoniazid were co-administered pyridoxine 10–25 mg daily. Standard dose rifampicin (600 mg if >50 kg, 450 mg if <50 kg) was prescribed except with single or “boosted” protease inhibitor containing regimens when rifabutin was given (150 mg daily or 150 mg three times per week, respectively). HAART was defined as use of ≥ 3 antiretroviral drugs in combination. Standard practice was to prescribe all drugs as daily self-administered treatment.

Analysis of data

Comparisons between groups were performed using either the χ^2 test or Fisher's exact test. The data were analysed using SAS version 8.2 (SAS Institute Inc, Cary, NC, USA).

RESULTS

One hundred and fifty six HIV infected individuals were treated for TB during the study period (TB+HIV+). The characteristics of these individuals and of a control group of

156 HIV uninfected individuals with tuberculosis (TB+HIV–) are shown in table 1.

In the TB+HIV+ group, the median CD4 count and HIV load at the time of starting anti-TB treatment was 77 (range 0–720) cells/ μ l and 5.1 log₁₀ (range 1.7–5.9) viral copies/ml respectively. One hundred and eleven of the 156 HIV infected individuals (71%) received HAART while on anti-TB treatment; 29 (26%) were already using HAART when anti-TB treatment was started and the remaining 82 commenced HAART a median of 2 (range 0–8) months later.

Treatment interruptions and common serious (grade III/IV) adverse events are described in table 2. Serious adverse events occurred in 63 of 156 (40%) TB+HIV+ individuals and in 41 of 156 (26%) TB+HIV– individuals ($p = 0.008$). The most frequent adverse event in TB+HIV+ individuals was peripheral neuropathy, which occurred in 22 (14%) compared with 3 (2%) of those without HIV co-infection ($p < 0.0001$). Of these 22 TB+HIV+ individuals, 17 were receiving concomitant HAART and 11 used regimens containing the nucleoside reverse transcriptase inhibitors (NRTI) stavudine (d4T) and/or didanosine (ddI). However, excluding those who received ddI and/or d4T in whom the only adverse event was peripheral neuropathy, the overall frequency of adverse events was little changed at 38%. In both TB populations hepatotoxicity developed in 20 (13%) of 156 individuals, all of whom were symptomatic. Only one case of hepatotoxicity occurred in an individual with hepatitis B co-infection and none were associated with hepatitis C co-infection.

Rash occurred frequently and with a similar incidence in both groups. Persistent vomiting was significantly more common among TB+HIV+ individuals ($p = 0.006$), and a greater number of TB+HIV+ individuals had more than one serious adverse event than in the TB+HIV– population ($p = 0.02$, table 2).

Interruption of anti-TB treatment occurred in 13% of TB+HIV+ individuals and 15% of TB+HIV– individuals ($p = 0.74$). In TB+HIV+ individuals, 17 of 20 (85%) interruptions were secondary to hepatotoxicity. Other causes were rash ($n = 2$) and peripheral neuropathy ($n = 1$). Among the TB+HIV– individuals, 20 of 23 (87%) interruptions were secondary to hepatotoxicity; the other three were due to thrombocytopenia, vomiting, and optic neuritis.

In both TB+HIV+ and TB+HIV– groups almost all interruptions in anti-TB treatment occurred within the first 2 months. There was a median delay of 4 weeks before full anti-TB treatment could be restarted. All such interruptions lasted for at least 1 week. HAART was discontinued in 11 of 111 TB+HIV+ individuals (10%) while they were receiving anti-TB treatment (four due to HAART related adverse events (three had immune reconstitution inflammatory syndrome) and seven due to virological failure). In a further 12 individuals (11%) the HAART regimen was altered during the course of anti-TB treatment.

Comparison of the frequency of both adverse events and interruptions in anti-TB treatment in the black African population showed that these were twice as high in the HIV+TB+ group as in the TB+HIV– group (43% v 21% for adverse events ($p = 0.07$); 13% v 6% for treatment interruption ($p = 0.03$)). In the white population the frequency of adverse events and treatment interruptions were similar in those with and without HIV co-infection (38% v 32% for adverse events; 17% v 19% for treatment interruption). It was not possible to perform a similar comparison in the Asian population as the number of HIV infected subjects was very small. Asian TB+HIV– individuals showed high rates of both adverse events (33%) and interruptions in anti-TB treatment (22%; all due to hepatotoxicity).

In the 82 HIV+TB+ individuals who started HAART after anti-TB treatment, 32 did so within 2 months (median

Table 1 Comparison of HIV infected individuals with TB and a control group of HIV uninfected patients with TB

	HIV infected (n = 156)	HIV uninfected (n = 156)
Median (range) age (years)	35 (20–73)	33 (16–82)
Male sex	81 (52%)	90 (58%)
Ethnicity		
Black African	122 (78%)	64 (41%)*
Asian	3 (2%)	45 (28%)
White	28 (18%)	47 (30%)
Other	3 (2%)	0 (0%)
Pulmonary TB	89 (57%)	80 (51%)
Median (range) duration of anti-TB treatment (months)	6 (1–24)	6 (1–36)
Discontinuation of anti-TB treatment	9 (6%)	6 (4%)
Incidence of TB recurrence	5 (3%)	2 (1%)
Incidence of hepatitis B or C co-infection	5 (3%)	5 (3%)

* $p < 0.0001$.

Table 2 Incidence of serious (grade III or IV) adverse events (AE) during the treatment of TB according to HIV status

	HIV infected (n = 156)	HIV uninfected (n = 156)	p value
Individuals with at least one AE	63 (40%)	41 (26%)	0.008
Hepatotoxicity	20 (13%)	20 (13%)	1.00
Peripheral neuropathy	22 (14%)	3 (2%)	<0.0001
Rash	20 (13%)	13 (8%)	0.20
Persistent vomiting	15 (10%)	3 (2%)	0.006
Arthralgia	6 (4%)	1 (1%)	0.07
Individuals with more than one AE	11 (7%)	2 (1%)	0.02
Individuals requiring interruption of anti-TB treatment	20 (13%)	23 (15%)	0.74

(range) CD4 count 40 (10–390) cells/ μ l) and 50 started after 2 months (median (range) CD4 count 52 (10–400) cells/ μ l). The frequency of adverse events in those starting HAART within 2 months and after 2 months was 53% and 48%, respectively; treatment interruptions occurred in 16% and 18%, respectively. No differences were noted in the occurrence of adverse events or treatment interruption whether HAART was started before anti-TB treatment, within or after 2 months of starting anti-TB treatment, or not at all ($p = 0.73$ for adverse events; $p = 0.55$ for interruption). In this group 56 of 82 had a CD4 count at TB diagnosis of <100 cells/ μ l, and the frequency of adverse events and treatment interruptions in these individuals was 52% and 16%, respectively. Twenty six of 82 had a CD4 count at TB diagnosis of >100 cells/ μ l with a frequency of adverse events and treatment interruptions in these individuals of 48% and 22%, respectively ($p = 0.74$ for adverse events; $p = 0.84$ for treatment interruption).

Five HAART regimens were prescribed (involving 31 different combinations of drugs). The five regimens were: nucleoside reverse transcriptase inhibitor (NRTI); two or three NRTI + non-nucleoside reverse transcriptase inhibitor (NNRTI); two or three NRTI + single protease inhibitor (PI); two or three NRTI + boosted PI; and two or three NRTI + NNRTI + PI (table 3). The frequency of adverse events, hepatotoxicity, and interruptions in anti-TB treatment were assessed in the 111 TB+HIV+ individuals according to the regimen of HAART prescribed. No differences were seen in the frequency of events with different regimens, although the numbers in some groups were small.

DISCUSSION

Our data show that, despite the fact that treatment of TB was associated with a greater frequency of serious (grade III/IV) adverse events in HIV co-infected individuals than in patients with TB alone (40% *v* 26%), this did not translate into an increased frequency of treatment interruptions (which occurred in approximately one in seven subjects). These findings did not appear to be altered by the level of

immunosuppression, the type of HAART regimen prescribed, or its time of initiation.

The most common reason for interrupting anti-TB treatment was hepatitis. This occurred mainly within the first 2 months of treatment, with a median time off anti-TB treatment of 4 weeks. Thus, most interruptions necessitated full re-treatment. In contrast with other reports, we found this to occur at a similar frequency in both HIV infected and uninfected patients.⁹ The difference in study results may reflect the criteria used to perform liver function tests, as well as the point at which treatment would be discontinued given an abnormal result. We used national guidelines which combine both blood test results and symptoms in deciding whether to repeat liver function tests.⁷ These are formulated primarily for HIV uninfected TB individuals, and it is likely that HIV infected individuals with TB tend to undergo more frequent blood tests.

Previous studies have identified a number of risk factors for anti-TB treatment induced hepatitis including disease extent, chronic hepatitis, and alcohol use.^{9–12} Both groups had a low prevalence of chronic viral hepatitis which made assessment of this as a risk factor unfeasible. We did not assess the extent of disease but sought to minimise the possibility that, early in the study, only the sickest patients were tested for HIV by identifying the HIV uninfected cohort in reverse time order. In most cases the use of alcohol, recreational drugs, and over-the-counter preparations was poorly recorded in the notes, and we felt that findings based on incomplete data might be misleading.

Only in the black African population did ethnicity appear to be important, with a significantly lower frequency of anti-TB treatment interruption observed in the HIV uninfected group than in the HIV infected group. The effect of ethnicity in this area is not well described but our data suggest that it may be important. Ethnicity may be one explanation for the marked difference in the observed frequency of hepatotoxicity necessitating treatment interruption in our series, compared with 3.2% in the UK study by Ormerod and Horsfield¹³ in which 70% of the subjects were Asian.

Table 3 Incidence of serious (grade III or IV) adverse events, hepatotoxicity, and interruptions in anti-TB treatment according to HAART regimen (n = 111)

Type of HAART regimen	No of patients receiving regimen	Serious adverse events	Hepatotoxicity	Interruptions to anti-TB treatment
Triple NRTI	9	5 (56%)	2 (22%)	2 (22%)
2NRTI + NNRTI	69	31 (45%)	9 (13%)	8 (12%)
2NRTI + PI	11	5 (45%)	2 (18%)	2 (18%)
2NRTI + "boosted" PI	13	5 (38%)	0 (0%)	0 (0%)
2NRTI + PI + NNRTI	5	2 (40%)	1 (20%)	1 (20%)
Not recorded	4	0 (0%)	0 (0%)	0 (0%)

NRTI, nucleoside reverse transcriptase inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; PI, protease inhibitor.

An earlier study of the treatment of HIV/TB co-infection in the era of HAART observed an incidence of significant adverse events of more than 50% with one third of subjects discontinuing anti-TB treatment.⁶ However, it did not contain an HIV uninfected comparator population which makes it difficult to assess the relative contributions of HIV, HAART and anti-TB treatment.

A large proportion of the excess adverse event rate in HIV/TB co-infected individuals was due to peripheral neuropathy. We expected some of this to result from co-administration of d4T or ddI with isoniazid, which is now not recommended due to a reported increase in neuropathy.^{14, 15} However, removal of those who received d4T/ddI and isoniazid from the analysis did not substantially reduce the observed incidence, which suggests the importance of other factors such as HIV itself.¹⁶

The retrospective collection of data meant that some adverse events may not have been recorded. However, rates of under-reporting should have been similar regardless of HIV status. Adherence was not formally assessed but we believe that it was generally very good—reflected in the high rates of treatment completion, a low rate of relapse of TB, and the good virological response to HAART (reported elsewhere¹⁷). Other limitations of our study include potential bias due to ethnic mix, difficulties in assessing the extent of TB disease as well as alcohol and other drug use, and the different frequency of blood test monitoring between groups.

In conclusion, our data suggest that, despite a higher frequency of serious (grade III/IV) adverse events during anti-TB treatment in individuals with HIV co-infection, treatment interruption occurs no more frequently than in HIV uninfected patients with TB.

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Funding: none.

Competing interests: none declared.

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